The claimed invention

The claimed invention is to a method of preventing depletion of non-autologous hematopoietic cells. This invention is based on Applicants' novel observations that non-autologous hematopoietic cells are rapidly cleared from the periphery of host animals, that macrophages play an important role in this clearance and that depletion of macrophages ameliorates this problem. This phenomenon and the role played by macrophages was not known until the Applicants showed that the elimination of endogenous macrophages in SCID mice resulted in the ability of non-autologous hematopoietic cells to circulate and survive in the periphery.

The phenomenon of rapid clearance of non-autologous hematopoietic cells occurs even in an immunocompromised host, potentially hindering the use of allogeneic cell transfusions in immunocompromised humans. Similarly, the potential of the extremely valuable SCID-hu mouse model has been limited due to low engraftment of human cells. The ability to enhance and prolong circulation of non-autologous hematopoietic cells thus is of vital importance in therapy and increases the potential for studying human hematopoietic, immunologic and disease processes *in vivo*. This ability also promises to contribute to vaccine development, more thorough understanding of immunologic reactions to tumors and development of human hybridomas.

Rejection under § 112, first paragraph

The specification is objected to and claims 1-12 and 14-31 are rejected under 35 U.S.C. § 112, first paragraph, as non-enabling for a variety of asserted grounds. Regarding claims 1-12 and 14-31, the Examiner contends that these claims must be limited to a non-human animal because the specification allegedly fails to provide the guidance necessary to show that the invention would work in humans. Regarding claims 10 and 11, the Examiner asserts that these claims must be limited to Cl_2MDP treatment on the ground that radiation therapy and chemotherapy could, under certain circumstances, possibly ablate the entire endogenous immune system, rending Cl_2MDP treatment moot. Regarding claim 31, the Examiner contends that the specification fails to define ablating "in whole or in part" the endogenous stem cell population of

the host animal. Each of these grounds either requests a standard far greater than that required by patent law or information already supplied in the specification and reiterated herein. The specification thus satisfies the requirements of and claims 1-12 and 14-31 are thus patentable under 35 U.S.C. § 112, first paragraph.

A. Claims 1-12 and 14-31

The Examiner states that claims 1-12 and 14-31 must be limited to a non-human animal. This is essentially a request for human clinical data. There is no basis in patent law for this requirement. Proof that the claimed invention actually works in humans is not necessary to satisfy § 112, first paragraph. See In re Brana 34 USPQ2d 1436 (Fed. Cir. 1994); Scott v. Finney, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office proceedings").

Rather than requiring proof of efficacy in humans, the PTO "bears the initial burden of setting forth reasonable explanation as to why it believes that the scope of protection provided by [the] claim[s] is not adequately enabled by the description of the invention provided in the specification." In re Wright, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). This reasonable explanation must include "sufficient reasons for doubting any assertions in the specification as to the scope of enablement." Id. The Examiner has provided no reasonable basis for doubting statements made in the application.

In requiring that the specification teach that the claimed invention works (and exactly how it works) in humans in order for the claimed invention to be enabled, the Examiner has imposed an overly-stringent and impermissible standard of enablement. The specification clearly discloses that the claimed invention is applicable to humans, and provides supporting data from an acceptable animal model. Acceptance the specification by the PTO as presumptively correct is a well-settled principle. In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995).[1]

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[1] "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971) (emphasis in original).

The Examiner states that the claims must be limited to a non-human animal "since the specification fails to provide the guidance necessary to show the invention would work as claimed in humans." Page 2. The Examiner asserts that the Applicants have failed to provide guidance regarding route of administration, amount, time course, and number of treatments. The specification does provide such guidance. See specification at page 10, lines 24-35, and page 11, lines 1-2. As discussed above, Applicants are under no obligation to show that the claimed invention works in humans. Insisting on such data is essentially a § 101 rejection on grounds which have been repeatedly found to be too stringent. For a summary of pertinent case law, see In re Brana and the Guidelines for Examination of Applications for Compliance with the Utility Requirement.

Moreover, even if no such guidance regarding dosages and routes of administration were provided, the specification and claims would still satisfy the requirements of § 112, first paragraph. In order to shift the burden of proof to the Applicants, the Examiner must provide a reasonable basis for doubting statements made in the application, or provide reasoning as to why one skilled in the art would doubt the asserted scope of the invention. In cases where therapeutic utility is in question, all that is necessary is to show credible results in an acceptable animal model system. In refusing to accept the animal model results as supporting the broadly claimed invention, the Examiner is essentially requesting that human data be provided. In allowing claim 13, the Examiner apparently is not calling into question the credibility of the results, or the acceptability of the animal model chosen for study. It is undisputed that SCID mice are accepted by those of skill in the art as reflective of the human immune system.[2] A § 103 reference

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[2] Kuby, "Immunology" (1992) W.H. Freeman and Co. pp.454-455, states: "Interest in scid mice has mushroomed recently with the development of a new way to utilize these mice to study the human immune system. Implantation in scid mice of portions of human fetal liver, thymus, and lymph nodes causes the mice to become populated with mature human T and B lymphocytes. Because the mice lack mature T and B cells of their own, they do not reject the transplanted human tissue. The fetal liver provides a source of human stem cells, which mature into human B and T lymphocytes within the human thymus and lymph node implants. Because the human T cells are exposed to mouse major histocompatibility antigens while they are still immature within the human thymus implant, they later recognize mouse cells as self and do not mount an immunologic response against the mouse host. The beauty of this system is that it enables one to study human lymphocytes within an animal model. . . . [T]he SCID-human mouse is rapidly becoming an important animal model for the study of immune depletion in AIDS."

provided by the Examiner, Aldrovandi et al., discuss the usefulness of this animal model system. The Examiner herself acknowledges the credibility of the animal model system by quoting "that the model may prove to be important for examining how HIV-1 infection interferes with ontogeny of the human immune system." Office Action, Page 5; line 6 (emphasis added).

The specification discloses that diminishing the number of endogenous macrophages prevents depletion of non-autologous hematopoietic cells in the SCID-hu mouse model system. Page 5, line 29 to page 6, line 6; Example 8. Based on these observations, one of skill in the art would find it credible that this would apply to humans. Having provided no reasons why one skilled in the art would reasonably doubt the specification disclosure, the Office has not met its initial burden of challenging a presumptively correct assertion in the disclosure. See In re Marzocchi, 169 USPQ 370 ("[I]t is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.") (emphasis in original). There has been no evidence presented that one skilled in the art would doubt that claimed method would work in humans. Nothing in the nature of the invention itself would lead one skilled in the art to reasonably doubt the scope of the claimed invention. The claimed invention is in accord with established scientific beliefs. There is no evidence, and none is provided, to show that the assertions made by Applicants are contrary to scientific principles. Applicants have not suggested "an inherently unbelievable undertaking or involve[d] implausible scientific principles." In re Brana at 1441.

In her discussion of the alleged non-enablement of claims 1-12 and 14-31, the Examiner also asserts, without support, that "the relationship between HIV infection and macrophage depletion is not elucidated in the specification and HIV infection in conjunction with DMDP treatment would appear to result in depletion, not prevention of depletion, of non-autologous hematopoietic cells." Page 2. Applicants respectfully request support for this assertion.[3] Absent support for this assertion, Applicants do not bear the burden of proof.

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[3] 37 CFR § 1.107(b) states: When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.

Nevertheless, the specification shows that the problem of rapid clearance of non-autologous hematopoietic cells occurs even if an animal is immunocompromised. Page 1, lines 15-17; page 5, lines 29-34. HIV infection results, inter alia, in an immunocompromised host. Applicants have found that clearance of non-autologous hematopoietic cells in an immunocompromised host (SCID mouse) was diminished upon treatment with Cl_2DMP. Based on this observation, it is reasonable for one skilled in the art to expect that use of Cl_2DMP in an HIV-infected patient would result in diminution of non-autologous hematopoietic cell depletion, rather than the contrary, as the Examiner contends.

B. Claims 10 and 11

Regarding claims 10 and 11, the Examiner states that the claims must be limited to Cl_2DMP treatment "since both radiation therapy and chemotherapy would possibly ablate the entire endogenous immune system, thereby rendering the DMDP treatment moot." The standard for enablement does not rest on the requirement that the claimed invention be applicable in all possible situations. The Examiner is addressing situations in which the invention is not called for (i.e., not indicated) because the desired result (i.e., depletion of macrophages) has already occurred. A claimed invention does not become unpatentable simply because there may be instances where the invention may not be required or indicated. The Examiner's own qualified language, that radiation therapy and chemotherapy could possibly ablate the entire endogenous immune system, itself acknowledges that the invention is indeed applicable in other instances besides the attenuated one postulated.

The Examiner contends that the specification "fails to provide guidance to one of ordinary skill regarding the types and protocols of chemotherapy or radiation therapy which would transiently immunocompromise the host immune system and yet allow the DMDP treatment to kill macrophages." Page 3. Methods of radiotherapy and chemotherapy are well-known in the art and need not be taught in the specification. Applicants are not required to provide information known to one of skill in the art at the time the application was filed. See, e.g., In re Buchner, 18 USPQ2d 1331 (Fed. Cir. 1991) ("The specification need not disclose what is well known in the art."). There are enumerable chemotherapy and radiation protocols known

in the art. Applicants need only provide guidance sufficient to enable one of skill in the art to make and use the invention as claimed. This requirement has been met.

The Examiner also notes that the specification fails to provide guidance as to the interaction of radiation/chemotherapy with Cl_2DMP treatment. As discussed above, the problem of rapid clearance of non-autologous hematopoietic cells occurs even if an animal is immunocompromised. Applicants made this observation in such a system (the SCID mouse). Page 5, lines 29-34; Examples 6 and 8. Treatment with Cl_2DMP prevents the rapid clearance of non-autologous hematopoietic cells in SCID mouse. Thus, it is not unreasonable to apply the method of preventing depletion of non-autologous hematopoietic cells by decreasing the number of macrophages to an immunocompromised host, regardless of the mechanism by which the host is immunocompromised, e.g., due to radiation or chemotherapy.

The Examiner goes on to state that "[t]he methods of radiation and chemotherapy ablate dividing cells and therefor would ablate all mature, immature and progenitor cells and would therefor ablate the macrophages as well." Page 3. As noted in the specification, one of the drawbacks of bone marrow transplants (BMT) is the lag time between transplantation and the production of lymphocytes. The morbidity and mortality rate in this period is quite high. It would be helpful to be able to augment BMT therapy by infusion of allogeneic lymphocytes. As it has how been found that any residual, non-hepatic portal, macrophages may prematurely deplete such lymphocytes, the claimed invention is clearly enabled. Applicants also respectfully point out that regimens of radiation therapy and chemotherapy vary widely and the conclusory statement that these methods "would ablate all mature, immature, and progenitor cells" simply does not reflect the typical situation. Further, even if in certain rare instances macrophages were ablated by radiation therapy or chemotherapy, this does not render the claimed invention unpatentable under § 112. Rather, as the Examiner herself indicates, such an instance might merely render the claimed invention "moot".

The Examiner also states that the specification "fails to present evidence that the combination of systems [radiation/chemotherapy and macrophage depletion] would result in depletion of macrophages." As discussed above, Applicants need not provide evidence that the claimed invention works in order to satisfy the enablement requirement. Rather, the Examiner must provide proof that one of skill in the art would doubt the truth or accuracy of the claimed

invention. This burden has not been met. Moreover, in the Examples, an immunocompromised animal (scid) is provided with non-autologous hematopoietic cells (SCID-hu thy/liv) in the presence or absence of endogenous macrophages (+/- Cl_2MDP) and is found to sustain non-autologous hematopoietic cells better in the absence of endogenous macrophages. Based on these observations, it is reasonable and credible to believe the truth and accuracy of the invention as broadly claimed.

C. Claim 31

Regarding claim 31, the Examiner points out that the specification does not disclose methods for ablating in whole or in part the endogenous stem cell population of the host animal. It is not clear if the Examiner is again requesting methods of ablating the hematopoietic system or requesting a definition of "in whole or in part." Such methods are well known in the art and thus need not be disclosed in the specification. The specification describes two methods of ablating an endogenous stem cell population in whole or in part, namely, radiation therapy and chemotherapy. The Examiner herself states that "both radiation therapy and chemotherapy would possibly ablate the entire endogenous immune system." Page 3, lines 2-4. The Examiner tacitly acknowledges this in noting that some treatments may result in total ablation, thus, some only partly ablate the hematopoietic system. If the immune system is possibly ablated then it is also possibly only partially ablated. If the confusion is with the phrase, Applicants submit that the common, literal meaning of the phrase should be sufficient to render it enabling.

According to the Examiner, "there are no known methods in the art which would preferentially ablate only the stem cells and not any of the other hematopoietic cells." Page 3 (emphasis added). The claimed invention does not recite ablation of only the stem cells, or ablation of non-dividing cells, as the Examiner appears to contend. The plain language of claim 31, which recites that the stem cells are ablated in whole or in part, not preferentially has been misconstrued. It is inappropriate to require that the specification disclose methods that are not indicated by the claims.

For these reasons, Applicants respectfully request withdrawal of the objection to the specification and the rejection of claims 1-12 and 14-31 under 35 U.S.C. § 112, first paragraph.

Rejection under § 112, second paragraph

Claims 1-23 and 31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Regarding claims 1-23 and 31, the Examiner contends that the term "substantially" is vague. However, the term is well accepted in patent law even without definition. In the present case however, the term has been carefully defined and thus is not vague. The specification on page 11, lines 3-11 defines "substantially":

> Substantially preventing depletion of non-autologous hematopoietic cells indicates that for at least several days, and preferably up to several weeks, the cells are found in the peripheral blood of the animal. Preferably 1% of the cells remain in the periphery after several days. More preferably 5% of the cells remain in the periphery after several days. Most preferably 10% of the cells remain in the periphery after several days.

Further, the specification describes how the number of non-autologous hematopoietic cells can be measured. Page 11, lines 12-23.

Regarding claim 31, the Examiner contends that the phrase "in whole or in part" is vague and unclear "since the metes and bounds of in part are not clear." Page 4. Applicants respectfully submit that the phrase "in whole or in part" has a clear, unambiguous meaning; that is, a "part" is anything that is less than the "whole." The phrase does not involve a term of art. One skilled in the art would understand what is claimed; thus, § 112, second paragraph is satisfied.

In view of these remarks, Applicants respectfully request that the Examiner withdraw her rejection of claims 1-23 and 31 under 35 U.S.C. § 112, second paragraph.

Rejection under § 103

Claims 1-31 are rejected under 35 U.S.C. § 103 as *prima facie* unpatentable as follows: (1) claims 1-17 and 19-23 are rejected as unpatentable over Aldrovandi et al. taken with Pinto et al.; (2) claim 18 is rejected as unpatentable over Aldrovandi et al. and Pinto et al. in view of Bernstein et al.; (3) claims 24-30 are rejected as unpatentable over Berenson et al. and Baum et al. taken with Pinto et al.; and (4) claim 31 is rejected as being unpatentable over Baum et al. taken with Pinto et al. In each instance, the Examiner assumes knowledge in the art of both the

problem and solution thereof by the claimed invention. Such an assumption is impermissible to establish unpatentability. The invention, and its purpose, cannot be assumed in the Examiner's inquiry. Such ex post facto reasoning is impermissible. In re Fine, 5 USPQ2d at 1600 (Fed. Cir. 1988).[4]

The Examiner contends that a combination of the references would produce the claimed invention. The only rationale given for this combination is unrelated to the claimed invention. It is well settled that the claimed invention must be found to be obvious, not some other, attenuated (and in this case, scientifically improbable) invention. Moreover, the claimed invention cannot be used to provide the impetus for combination of the references. Absent the information provided in the specification and the claimed invention, there would be no reason to combine the references. One of skill in the art, lacking the knowledge that endogenous macrophages play a role in depletion of non-autologous hematopoietic cells, would have no reason to combine the references or expect the result obtained.

"In rejecting claims under 35 U.S.C. § 103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness." In re Oetiker, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only upon establishment of obviousness are Applicants required to provide evidence or argument to counter that showing. Id. The Examiner has not met the burden of presenting a prima facie case of obviousness. The claims are thus patentable over the prior art of record and Applicants are under no obligation to present evidence to overcome the rejection.

As discussed herein, (supra, "The claimed invention", pages 2-3), Applicants have invented a method for preventing depletion of non-autologous hematopoietic cells as well as animal model system using this method. This method entails decreasing the number of endogenous macrophages concomitant with the introduction of non-autologous hematopoietic cells. The invention stems from Applicants' novel finding that macrophages play an important role in the rapid clearance of non-autologous hematopoietic cells. The cited prior art of record does not teach or suggest this correlation.

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[4] "to imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." Quoting W.L. Gore, 220 USPQ 303, 312-313 (Fed. Cir. 1983).

The claimed invention represents a significant advance in the ability to enhance and prolong circulation of non-autologous hematopoietic cells. Such an advance finds important applications in therapy as well as the study of hematopoietic, immunologic, and disease processes *in vivo*.

Importantly, the problem of rapid clearance of non-autologous hematopoietic cells is not addressed, disclosed, or even suggested by the Examiner's cited art . Absent even a recognition of the problem, how can it be said that the solution to the problem would be obvious? Aldrovandi et al. focus on the SCID-hu mouse as a possibly useful in vivo system for the study of HIV-1-induced pathology. Pinto et al. describe the prominent role of macrophages in host resistance to pathogenic microorganisms. Pinto et al. do not address, and do not concern themselves with, the problem of clearance of non-autologous hematopoietic cells. Bernstein et al. study the effect of stimulation of macrophages with LPS on HIV viral replication. Berenson et al. examine whether engrafted $CD34^+$ cells isolated from the marrow of cancer patients were capable of reconstituting hematopoiesis *in vivo*. Baum et al. address the problem of isolating a hematopoietic stem cell population.

None of the cited prior art references, either alone or in combination, disclose or suggest the claimed invention, which is directed to a method of preventing depletion of non-autologous hematopoietic cells by decreasing the number of endogenous macrophages.

A. Claims 1-17 and 19-23

Claims 1-17 and 19-23 are rejected as unpatentable over Aldrovandi et al. taken with Pinto et al. The Examiner maintains that "it would have been obvious to one of ordinary skill to modify the method of Aldrovandi by treating the SCID-hu mice with DMDP in order to kill the endogenous macrophages." As discussed below, this rationale does not provide the key consideration required for *prima facie* obviousness based on a combination of references: whether or not either reference suggests the problem solved by the Applicants and its solution, that is, decreasing macrophages in order to prevent depletion of non-autologous hematopoietic cells. Neither reference does so. Such a solution (killing macrophages) to this particular problem becomes evident only in light of Applicants' disclosure. Thus, the Examiner has improperly presumed knowledge of the problem, as well as the desirability of diminishing macrophages as the solution to the problem in combining the references.

As acknowledged by the Examiner, Aldrovandi et al. merely disclose that the SCID-hu mouse system may be an important model to study HIV-1 induced pathogenesis *in vivo*, further establishing the model system as credible to those skilled in the art. In reaching that conclusion, Aldrovandi et al. perform experiments which involve human fetal liver and thymus transplants which were later shown to be capable of being infected by HIV-1. Notably, Aldrovandi et al. also teach that human fetal Thy/Liv cells can be successfully transplanted in SCID mice. Aldrovandi et al. do not address or suggest the problem of rapid depletion of non-autologous hematopoietic cells, nor do they discuss or suggest any relationship between a SCID-hu system and the problem of rapid depletion of non-autologous hematopoietic cells.

Pinto et al. disclose the effects of dichloromethylene diphosphonate (Cl_2MDP) encapsulated in liposomes on antimicrobial resistance, particularly against infection with *Listeria monocytogenes* and herpes simplex virus type 2. Acknowledging the prior knowledge that treatment with liposome-encapsulated Cl_2MDP efficiently and selectively depletes splenic and liver macrophages (which Applicants also acknowledge in their specification on page 3, lines 1-4), Pinto et al. provide evidence that splenic and liver macrophages are important components of host antimicrobial resistance. The loss of non-autologous hematopoietic cells is essentially a graft rejection. The mechanisms of graft rejection are thought to be separate from and unrelated

to one another. Pinto et al. do not disclose or even suggest decreasing the number of macrophages as a method of preventing graft rejections broadly and preventing depletion of non-autologous hematopoietic cells specifically. Those of skill in the art would therefore not look to Pinto et al. for the solution to a graft rejection issue.

Additionally, Pinto et al. observe that double treatment with DMDP causes a marked leukocytosis (discussed below) and a marked decrease in NK activity. Notably, Pinto et al. find that administration of an immunomodulator restores much of the anti-microbial resistance in macrophage-depleted mice, prompting their suggestion that their observations "support the use of immunomodulators to enhance antimicrobial resistance in immunodeficient or immunosuppressed individuals." Page 585. The goal of enhancing antimicrobial resistance is unrelated to Applicants' goal of prolonging circulation of non-autologous hematopoietic cells, both mechanistically and conceptually. Immunity to pathogens and prevention of graft rejection (or, more specifically, prevention of rejection of non-autologous hematopoietic cells) involve disparate aspects of immunology.[5]

In order to combine references to establish prima facie obviousness, it has been acknowledged that "there must be some logic apparent from the positive, concrete evidence of the record which justified the combination of primary and secondary references." In re Stemniski, 170 USPQ 343, 346 (CCPA 1971). The mere fact that references could have been combined or modified does not render the invention obvious unless the prior art suggests the desirability of such modification. In re Imperato, 179 USPQ 730, 732 (CCPA 1973). See also In re Bergel, 130 USPQ 206, 208 (CCPA 1961) ("the mere fact that it is possible to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination") (emphasis in original). In this case, none of the Examiner's cited prior art contains the suggestion the combination of the record. A reference which describes (and praises) the mouse model system used by the Applicants and a reference

[5] Immunology references invariably discuss immunity to microorganisms and graft rejection separately. For instance, Kuby (1992) discusses immune response to infectious diseases in Chapter 19 (pages 419 to 439), while describing transplantation immunology in Chapter 22 (pages 487 to 501).

which identifies macrophages as important in host resistance to infection with Listeria monocytogenes or herpes simplex type 2 clearly do not provide sufficient, concrete evidence justifying the combination. In the case of the first reference, Applicants should not be penalized for using the best possible animal model system. In the second reference, the effect of macrophages on bacterial and viral immunity is unrelated to the claimed invention and cannot be extrapolated to the problem solved by the claimed invention.

The references of record differ significantly in terms of the problems addressed, both with respect to each other and with respect to the claimed invention. Aldrovandi et al. address the problem of studying the effect of HIV-1 infection on the human thymus. The problem Aldrovandi et al. attempt to solve (and succeed in solving) is that "[s]tudies of HIV-1 pathogenesis have been hampered by lack of a suitable animal model system." Page 732. As a result of their experiments in SCID mice, they speculate that the SCID-hu mouse "may be an important small animal model to study HIV-1 induced pathogenesis in vivo." Page 735. Aldrovandi et al. also note in closing that their newly developed model of HIV infection "may prove to be important for examining how HIV-1 infection interferes with the ontogeny of the human immune system." Page 735. Clearly, Aldrovandi's entire focus is on studying HIV infection per se. In stark contrast, Pinto et al. are concerned with the role of macrophages in natural immunity to microorganisms.

The cited art of record do not suggest the problem that the claimed invention solves, that is, preventing depletion of non-autologous hematopoietic cells. Further, the Examiner's cited art of record neither contains any indication that the disclosure of the other would be desirable for any reason. This is not surprising, considering the completely different problems and experimental approaches used.

Not only does the Examiner's cited art address problems completely different than that of the claimed invention; the entire thrust and findings of each reference belie any attempt to combine them for any reason. Aldrovandi et al. successfully transplant human fetal thymus and liver (Thy/Liv) into SCID mice (forming SCID-hu mice). The Thy/Liv transplants in turn are successfully infected with HIV virus (HIV-1), and the infected human tissue displays parameters typical of HIV infection. The xenographic Thy/Liv transplants in Aldrovandi et al. survive for over two weeks, allowing a successful conclusion to the experiment. If Aldrovandi et al. were

already successful, why would depletion of macrophages be indicated? If Aldrovandi et al. are interested in HIV infection per se, why complicate the experimental system by macrophage depletion?

Similarly, if Pinto et al. are interested in studying microbial resistance, why use a SCID mouse, which is severely immunocompromised? Pinto et al. observe that Cl_2MDP exerts an immunosuppressive effect with respect to microorganisms and suggest that using immunomodulators which counteract immunosuppression are indicated for immunocompromised or immunosuppressed hosts, rather than an agent that would immunocompromise these hosts still further.

The only possible rationale for the motivation to combine the references provided by the Examiner is in terms of treating HIV-1 infection by depleting macrophages. These are not the terms of the claimed invention, which is a method of preventing depletion of non-autologous hematopoietic cells by depleting macrophages. The Examiner contends that Aldrovandi et al. provide the motivation to combine the references because they disclose the SCID-hu mouse system as a model that "may prove important for examining how HIV-1 infection interferes with the ontogeny of the human immune system." Page 7. From this disclosure, the Examiner states that "it would have been obvious in view of those teachings to treat hosts having HIV-1 infection with DMDP since DMDP is known to inactivate macrophages, a known source of HIV infection, in order to abolish a viral reservoir." Page 7. This is not a proper or adequate basis for a § 103 rejection.

Applicants respectfully submit that treatment of HIV infection by depletion of endogenous macrophages is not the claimed invention. Nor does abolishing a viral reservoir have anything to do with the rationale of the aspect of the invention that includes depletion of macrophages in HIV-infected hosts. The fact that Examiner's rationale for combining these two references does not address the claimed invention, and the problem it solves, is further indication that combination of these two references is improper.

The Examiner also goes one step further than the teachings of the combined references in an effort to prove that the claimed invention is unpatentable over the prior art. From the observation that the combination of Aldrovandi et al. and Pinto et al. render obvious "treat[ing] hosts having HIV-1 infection with DMDP since DMDP is known to inactivate

macrophages, a known source of HIV infection, in order to abolish a viral reservoir," the Examiner extrapolates, without support, that it was "within the ordinary skill in the art" to "obtain a method of preventing depletion of non-autologous hematopoietic cells." Page 7. This begs the question. The Examiner cannot merely state that one of skill in the art could practice the claimed invention and, therefore, it was obvious to do so. The fact is that one of skill in the art could practice the claimed invention only upon reading the specification and claims. The mere fact that various components of the claimed invention are available in the art but without motivation or suggestion to combine is insufficient to establish unpatentability. The Examiner's reasoning reflects an inappropriate standard for prima facie obviousness. The question of obviousness is not whether a modification of a prior art reference was within the ordinary skill of the art. Obviousness is indicated only if the prior art suggests the claimed invention to one skilled in the art. The desirability of such a modification must also be suggested by the prior art. None of these aspects of obviousness are found in the Examiner's cited references. In fact, the gap left by the references with respect to the role of macrophages in depletion of non-autologous hematopoietic cells is striking evidence of non-obviousness. The prior art of record gives no indication that a) non-autologous hematopoietic cells are rapidly cleared from the periphery of host animals, b) macrophages are involved in the problem of rapid clearance of non-autologous hematopoietic cells, or c) that depletion of macrophages would have such a profound ameliorative effect on this problem.

In attempting to provide a rationale for combining the references, the Examiner repeatedly notes the observation by Pinto et al. that administration of Cl_2MDP causes leukocytosis. Applicants submit that this observation is one of several made by Pinto et al. Pinto et al. also observe a marked decrease in NK activity. Collectively, Pinto et al. summarize that, "support the use of immunomodulators to enhance antimicrobial resistance in immunodeficient or immunosuppressed individuals." Page 585 (emphasis added). Enhancing antimicrobial resistance is unrelated to the claimed invention, nor does this concept suggest the claimed invention. Further, the ramification of the leukocytosis observation is unclear, as admitted by Pinto et al. ("The mechanism involved in the peripheral blood leukocytosis caused by DMDP liposome treatment requires further study"; page 582). It cannot be taken, in light of

the claimed invention, to render the claimed invention obvious. This would be manifestly unfair use of hindsight.

Regarding leukocytosis, the Examiner also states that one skilled in the art "would also expect a stimulation of the [non]-autologous (human) lymphocytes in view of the leukocytosis effect seen by Pinto on the endogenous lymphocytes." Page 6 (emphasis added). This presupposes knowledge of the claimed invention. Besides there being no ground for extrapolating this observation into SCID mice, which are severely immunocompromised, the Examiner has not addressed what effect might occur on endogenous leukocytes, which is just as important a consideration in the claimed invention, which is directed to preventing depletion of non-autologous hematopoietic cells. There is no basis for extrapolating Pinto et al.'s findings, based endogenous leukocytosis in normal mice treated with Cl_2MDP, to non-autologous hematopoietic cells in a normal or immunocompromised animal. This is especially true in view of Pinto et al.'s own explanation for this phenomenon.

> The fact that the increase in circulating leukocytes occurred so rapidly and the fact that microscopy showed the cells to be mature argue against the leukocytosis being due to rapid mobilization of immature bone marrow cells. The leukocytosis may therefore be related to an outflow of the large circulating pool of lymphocytes and PMN that is contained within the spleen and liver, due to destruction of tissue M© and subsequent alterations in organ architecture. Page 582.

This explanation has its entire basis in the endogenous system; its very terms are contrary to extrapolation to the system that the invention addresses. In fact, the possibility of endogenous leukocytosis (which is, at most, what Pinto et al. suggest) would, if anything, warn against the claimed invention.[6]

Even if the Examiner's cited references were combined, they do not disclose or suggest the claimed invention. The Examiner provides an unrelated motivation to combine references on page 7 of the Office Action, in stating: "treat[ing] hosts having HIV-1 with DMDP, since DMDP is known to inactivate macrophages, a known source of HIV infection, in order to abolish a viral reservoir." This combined "teaching" is clearly not the claimed invention, which

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[6] Endogenous leukocytosis could interfere with the prevention of depletion of non-autologous hematopoietic cells, as the host could have more lymphocytes with which to mount an immune response. This possibility is more plausible than the one posited by the Examiner, given Pinto et al.'s observations and discussion.

is directed to a method of preventing depletion of non-autologous hematopoietic cells. Also, as discussed above, the references of record neither teach or suggest this combination, and it is unclear that one of skill in the art would apply a method for decreasing viral resistance to HIV infected individuals. Inactivation of macrophages in order to abolish a viral reservoir does not reflect the goal or rationale behind the claimed invention. At most, combination of Aldrovandi et al. with Pinto et al. teaches SCID-hu (Thy/Liv) mice infected with HIV and normal mice treated with Cl_2MDP. The references use drastically different mice strains; thus, extrapolation from Pinto et al. to the SCID-hu model system of Aldrovandi et al. is extremely problematic. It is hard to imagine what, if any, reasonable conclusion could be reached based on both disclosures, absent further experimentation. As discussed above, neither reference of record addresses the problem of rapid clearance of non-autologous hematopoietic cells. Importantly, the claimed invention "teaches advantages not appreciated or contemplated [by the prior art]." In re Fine, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988).

Regarding claims 2 and 15 (reciting "non-autologous hematopoietic cells are injected into the animal"), the Examiner apparently equates administration by transplantation with administration by injection. These merely represent differing modes of administering the non-autologous hematopoietic cells. For the same reasons discussed exhaustively above, the claimed invention is not obvious, regardless of the mode of administration.

Regarding claim 6 (reciting "macrophages are decreased genetically"), the Examiner contends that "the use of mice having naturally occurring low levels of macrophages would be obvious to one of ordinary skill since the purpose of the use of DMDP is to reduce the levels of macrophages." Page 6. This "purpose" that the Examiner provides is the claimed invention. By using the purpose of the invention ("to reduce the levels of macrophages") as a reason for finding an embodiment obvious, the Examiner has again presupposed knowledge in the art of the claimed invention. The invention, and its purpose, cannot be assumed in the Examiner's inquiry. Knowledge of the desirability of lowering the level of macrophages in order to prevent depletion of non-autologous hematopoietic cells only becomes clear upon Applicants' novel findings regarding this relationship. It cannot then be used against Applicants to find the claimed invention unpatentable.

Regarding claims 9 (reciting "the animal is human and the virus is human immunodeficiency virus") and 17 (reciting "the animal is human and the non-autologous hematopoietic cells are injected"), the Examiner states that "it would have been obvious to one of ordinary skill to apply the method of Aldrovandi modified by Pinto to humans having HIV infection since Pinto teaches that macrophage depletion interferes with the immune response and also stimulates lymphocyte production." Page 6. Pinto et al. disclose that macrophage depletion (by Cl_2MDP liposomes) significantly depresses microbial resistance in mice. As a major danger in HIV infection is opportunistic infection, the disclosure of Pinto et al. would if anything discourage an inventor from attempting to apply the claimed method to a human infected with HIV. In fact, Pinto et al. conclude that their findings "support the use of immunomodulators to enhance antimicrobial resistance in immunodeficient or immunosuppressed individuals." Page 585, column 1. Such an observation could hardly be said to suggest that one should instead diminish a population of cells in the immune system, as does the claimed invention.

Regarding claims 10 and 11 (reciting that the animal is immunocompromised due to radiation (10) or chemotherapy (11)), the Examiner states that "ablation of the immune system to deplete the host of immune responding cells would be obvious in view of the teachings of Aldrovandi that the host must be immunocompromised (SCID) in order to allow transplantation of non-autologous tissue." Page 7. This statement does not reflect analysis of the claimed invention, which is prevention of depletion of non-autologous hematopoietic cells by diminishing macrophages. For the reasons discussed above, the claimed invention is not obvious, whether or not the animal is further immunocompromised.

As already discussed, the Examiner's reasoning assumes knowledge of the invention. Such use of hindsight is impermissible. Only with the knowledge that decreasing macrophages prevents depletion of non-autologous hematopoietic cells can the Examiner state that an aspect of the claimed invention, namely, its application to an immunocompromised animal, is "obvious".

Regarding claims 19-23 (reciting a non-human animal), the Examiner reiterates the combination of Aldrovandi et al. and Pinto et al. as rendering obvious the claimed non-human mammal "since Aldrovandi discloses SCID-hu mice containing human hematopoietic cells and Pinto discloses use of DMDP to inactivate macrophages." Page 7. This, once again, presupposes

knowledge of the claimed invention. As discussed above, neither one of these references even slightly suggests the desirability of using what it discloses in combination with what is disclosed in the other, or the necessity or desirability of the claimed invention. Neither reference addresses the problem of preventing depletion of non-autologous hematopoietic cells. Nothing in the Aldrovandi et al. reference suggests the rapid clearance of non-autologous hematopoietic cells or its relationship to macrophages. Nor is this relationship addressed in Pinto et al. Absent knowledge of the claimed invention, one of skill in the art would have no reason to modify either of the references, or the combination thereof, to obtain the claimed invention. A reason that consists of the rationale of the claimed invention itself is impermissible hindsight.

The Examiner contends that Aldrovandi et al. provide the motivation to combine these references because "Aldrovandi discloses that 'The SCID-hu mouse system does not merely reproduce in vitro phenomenon, but allows infection of primary cells to be studied in a more appropriate environment. This model may prove to be important for examining how HIV-1 infection interferes with the ontogeny of the human immune system.'" Page 7. This provides little more than an acknowledgement of the credibility of the animal model system. Aldrovandi et al.'s pointed emphasis on the study of HIV infection is one of the reasons this reference provides no such motivation to combine.

The Examiner's statement that treating hosts having HIV with Cl_2MDP would have been obvious "since DMDP is known to inactivate macrophages, a known source of HIV infection, in order to abolish a viral reservoir" is contradicted by one of the references cited by the Examiner. Bernstein et al. disclose that activation of macrophages appears to decrease HIV replication. Such a teaching would hardly suggest to one skilled in the art that inactivation of macrophages in a host with HIV is desirable. Moreover, the Examiner that the claimed invention is not treating "hosts having HIV-1 infection", but rather is "a non-human mammal comprising human hematopoietic cells wherein the mammal contains a decreased level of endogenous macrophages sufficient to prevent substantial depletion of non-autologous hematopoietic cells" (claim 19).

For these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. Claim 18

Claim 18 is rejected as unpatentable over Aldrovandi et al. and Pinto et al., and further in view of Bernstein et al. The Examiner states that Aldrovandi et al. and Pinto et al. were applied to claims 1-18; however, these references were cited in rejecting claims 1-17 and 19-23 (page 5). The Examiner states that Bernstein et al. disclose that macrophage growth factors such as GM-CSF, M-CSF and IL-3 may enhance HIV replication in mononuclear phagocytes. The Examiner then contends that "it would have been obvious to one of ordinary skill then to inactivate macrophages as a method of treatment in order to abolish viral replication." Page 8. Regardless of whether this wold be obvious, it is not the claimed invention.

Claim 18 is to a method of treating an immunocompromised animal which includes administering an effective amount of non-autologous hematopoietic cells and decreasing endogenous macrophages. As discussed above, nowhere do Aldrovandi et al. and Pinto et al., either alone or in combination, disclose or suggest a method of treating an immunocompromised animal, or administering non-autologous hematopoietic cells in conjunction with decreasing endogenous macrophages. In light of the failure of Aldrovandi et al. and Pinto et al. to render the claimed invention unpatentable, subsequent references cannot make up the deficiency.

Even if a combination of references based on the motivation to practice an invention other than, and unrelated to, the claimed invention were proper, the rationale given here is not even scientifically credible. Bernstein et al. disclose that activation of monocyte-derived macrophages with lipopolysaccharide (LPS) decreases HIV replication. Given this, the Examiner's statement that it would be obvious to "inactivate macrophages as a method of treatment in order to abolish viral replication" is without support. Further, the claimed invention is to decreasing macrophages, not inactivation of macrophages. Moreover, "abolishing viral replication" does not reflect the rationale of the claimed invention.

Further, nowhere do Bernstein et al. address the problem of treating an immunocompromised animal with non-autologous hematopoietic cells. Nor do Bernstein et al. disclose administering non-autologous hematopoietic cells. The problem that Bernstein et al. attempt to solve is the effects of stimulation of mature primary monocyte-derived macrophages

on HIV replication, which is not even distantly related to the problem of rapid clearance of non-autologous hematopoietic cells.

As a rationale for combining the references, the Examiner contends that Bernstein et al. provide the motivation to combine because they disclose that macrophage growth factors may enhance HIV replication in mononuclear phagocyte. Such a basis for motivation to combine completely ignores both the claimed invention and the main point of the Bernstein et al. reference, which is that activation of macrophages decreases HIV replication.

The combination of Aldrovandi et al., Pinto et al., and Bernstein et al. do not disclose or suggest the claimed invention, as the above discussion makes clear. For these reasons, Applicants respectfully request withdrawal of this rejection.

C. Claims 24-30

Claims 24-30 are rejected as unpatentable over Berenson et al. and Baum et al. taken with Pinto et al. These claims are directed to a method of restoring hematopoietic cells to an immunocompromised human including the steps of administering an effective amount of human peripheral blood cells in conjunction with decreasing endogenous macrophages.

As the Examiner states, Berenson et al. disclose administration of $CD34^+$ marrow cells to humans after receiving marrow-ablative therapy. In contrast with the claimed invention, however, the cells used were autologous. Page 1718. Baum et al. disclose that the $CD34^+$ population contains stem cells (rather than is stem cells, as the Examiner states).

The Examiner acknowledges that neither Berenson et al. nor Baum et al. disclose decreasing endogenous macrophages, as is claimed. However, the Examiner contends that this significant gap is purportedly filled by Pinto et al. Again, this presupposes knowledge of the claimed invention, as the Examiner assumes knowledge of the mechanism described only by the Applicants' claimed invention. In the absence of the claimed invention, one skilled in the art would not be motivated to combine Pinto et al. with either of Berenson et al. or Baum et al. Berenson et al. infuse $CD34^+$ cells into patients after myeloablative therapy. According to the Examiner, such treatment "would possibly ablate the entire endogenous immune system, thereby rendering the DMDP treatment moot." Page 3. Baum et al. merely disclose that a $CD34^+$

population contains stem cells. There is no apparent connection between Baum et al. and Pinto et al. and none is provided by the prior art of record.

In supporting the motivation to combine the above references, the Examiner states that "[o]ne of ordinary skill would be interested in treating an HIV patient with DMDP since DMDP stimulates lymphocyte proliferation and HIV-1 patients are deficient in $CD4^+$ T cells." Page 9. Mere interest in performing an experiment for an unrelated reason does not render an invention obvious. Moreover, this statement completely ignores the principle observation of Pinto et al., namely, that administration of Cl_2MDP causes a significant decrease in antimicrobial resistance. As discussed above, an equally important concern regarding HIV infection (or any other immunocompromised state) is the susceptibility to opportunistic infection. The disclosure by Pinto et al. certainly does not suggest the desirability of further compromising the immune system of an animal already in that condition, especially using an agent (Cl_2MDP) that causes a decrease in antimicrobial resistance.

For these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

D. Claim 31

Claim 31 is rejected as unpatentable over Baum et al. taken with Pinto et al. Claim 31 is to a method of improving engraftment efficiency for transplantation of a population of non-autologous hematopoietic stem cells in an animal including ablating the endogenous stem cell population of the host and transplanting stem cells into the host in conjunction with decreasing endogenous macrophages in the host.

In supporting her contention of obviousness, the Examiner acknowledges that Baum et al. "fail to disclose decreasing endogenous macrophages." Page 9. Again, Pinto et al. are cited as "curing the deficiency." The Examiner cannot pick and choose the elements of the claimed invention from the prior art on the basis of the claims themselves. This does not support a prima facie obviousness rejection. As discussed above, however, there is no motivation to combine the references, absent the knowledge provided by the claimed invention. Baum et al. merely disclose that the $CD34^+$ population contains stem cells. Pinto et al. disclose that treatment with Cl_2MDP diminishes antimicrobial resistance. Neither reference of record

addresses the problem of preventing depletion of non-autologous hematopoietic cells. Neither reference suggests that the disclosure of one would be desirable with the other, absent knowledge of Applicants' observations. A reference that discloses a population of cells containing stem cells and engraftment of allogeneic cells bears no relation to a reference that addresses the problem of the role of macrophages in antimicrobial resistance. Furthermore, the reference does not even provide the problem to be solved, much less the solution.

In supporting her contention of motivation to combine the above references, the Examiner states that "[i]t would have been obvious to one of ordinary skill to modify the method of Baum by using DMDP in view of the teachings of Pinto that DMDP causes leukocytosis of lymphocytes and PMN and otherwise augments the immune responses by diminishing the humoral immune response, thereby prolonging the life of the engrafted tissue." Pages 9-10. As discussed above, Pinto et al.'s observation of leukocytosis pertains to the endogenous system of an otherwise healthy animal, not non-autologous hematopoietic stem cells in a host animal lacking endogenous stem cells.

In view of the above discussion, reconsideration and withdrawal of the 35 U.S.C. § 103 rejection is respectfully requested.

Conclusion

Applicants submit that all issues raised in the Office action have been properly addressed in this response. Accordingly, allowance and issuance of the pending claims is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to our Deposit Account No. 03-1952. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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Date: December 6, 1995

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